Closed-loop effects in coupling cardiac physiological models to clinical interventions

Dirk Husmeier[1] and L. Mihaela Paun[1]

[1] School of Mathematics & Statistics, University of Glasgow, Scotland, UK

E-mail for correspondence: dirk.husmeier@glasgow.ac.uk

Abstract: There have been impressive methodological advancements in the mathematical modelling of cardio-physiological processes. The majority of recent articles have focused on the *forward problem*: developing flexible mathematical models and robust numerical simulation procedures to match characteristics of physiological target data, and the *inverse problem*: inferring model parameters from cardiac physiological data with reliable uncertainty quantification. However, when connecting mathematical model predictions to the clinical decision process, new challenges arise. This paper briefly discusses the complications that potentially result from *closed-loop* effects, and the model extensions that are required to reduce the ensuing bias.

Keywords: Closed-loop effect, physiological model, pulmonary hypertension

1 Introduction and illustration

Consider a random variable $X \in \mathbb{R}$ that represents the value of a clinical disease indicator. Based on some adequate clinical data, which for the purpose of the following discussion do not need to be made specific, we monitor its posterior distribution $p(x)$ and the risk of the clinical indicator exceeding some tolerance threshold

$$P(X > \tau) \; = \; \int_{\tau}^{\infty} p(x)dx \tag{1}$$

If this risk exceeds some critical value α, $P(X > \tau) \; > \; \alpha$, medical treatment, for instance in the form of medication, is provided. While potentially only aiming at a symptomatic relief, this treatment is assumed to interfere with the patient's physiology or pathophysiology and affect the clinical disease indicator. Let $Y \in \mathbb{Y}$ denote a random variable that represents the

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value of the disease indicator upon medical intervention, and let f describe the effect of the treatment: $y = f(x)$. This treatment effect implies a transformation of the probability distribution of the disease indicator:

$$p_y(y) = \int_{-\infty}^{\infty} \delta\Big(y - f(x)\Big) p_x(x) dx \tag{2}$$

where $\delta(.)$ is the Dirac delta function. The consequence is a potential prediction bias:

$$P(Y > \tau) \;=\; \int_{\tau}^{\infty} p(y) dy \;\neq\; P(X > \tau) \;=\; \alpha \tag{3}$$

which needs to be accounted for in the clinical decision process. As a simple illustration, assume the posterior distribution of the clinical indicator prior to the medical intervention is normal, $p_x(x) = N(x|\mu, \sigma^2)$, with mean $\mu = 0$ and variance $\sigma^2 = 1$, and that the effect of the medical treatment is a shift of the clinical indicator by $\psi \in \mathbb{R}^+$:

$$f(x) = \left[\begin{array}{ll} x & \text{if } x \leq \tau \\ x - \psi & \text{if } x > \tau \end{array} \right. \tag{4}$$

We obtain $p(y)$ by inserting (4) into (2) and making use of the following feature of the Dirac delta function:

$$\delta\Big(y - f(x)\Big) \;=\; \sum_i \frac{1}{|f'(x_i)|} \delta(x - x_i) \tag{5}$$

where $\{x_i\}$ are the roots of $y - f(x) = 0$. Inserting (4) and (5) into (2) gives:

$$p_y(y) \;=\; \left[\begin{array}{ll} p_x(y) & \text{if } y < \tau - \psi \\ p_x(y) + p_x(y + \psi) & \text{if } \tau - \psi \leq y \leq \tau \\ p_x(y + \psi) & \text{if } y > \tau \end{array} \right. \tag{6}$$

The apparent probability of the disease indicator to exceed the critical threshold τ will therefore be evaluated as

$$P(Y > \tau) = \int_{\tau}^{\infty} p_y(y) dy = \int_{\tau}^{\infty} p_x(y+\psi) dy = \int_{\tau+\psi}^{\infty} N(y|0,1) dy = \overline{G}(\tau+\psi)$$

where $\overline{G} = 1 - G$ and $G(.)$ is the normal cumulative distribution function, whereas the actual probability is

$$P(X > \tau) \;=\; \int_{\tau}^{\infty} p_x(x) dy \;=\; \int_{\tau}^{\infty} N(y|0,1) dy \;=\; \overline{G}(\tau) \tag{7}$$

Since $\overline{G}(.)$ is strictly monotonously decreasing, $\overline{G}(\tau + \psi) < \overline{G}(\tau)$, the apparent probability is biased and systematically underestimates the risk of exceeding the critical threshold τ: $P(Y > \tau) < P(X > \tau)$. Hence, by ignoring the effect of the treatment on the clinical indicator variable, any clinical decision support system based on this indicator variable will systematically underestimate the patient's state of risk.

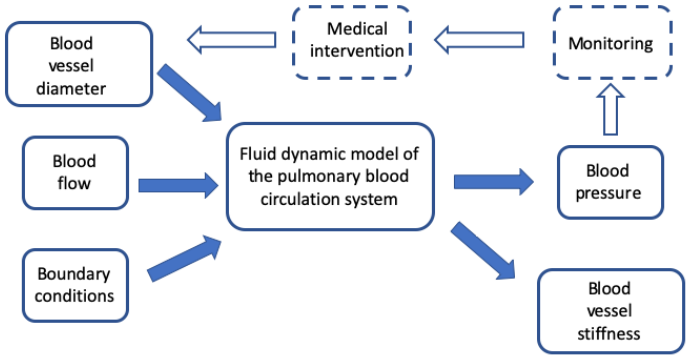

FIGURE 1. Schematic representation of our physiological model of pulmonary hypertension and how it is affected by closed-loop effects following a clinical intervention. See the main text for details.

2 Physiological application: pulmonary hypertension

Pulmonary hypertension, i.e. high blood pressure in the lungs, is a major risk factor for a variety of medical conditions, including inadequate coronary perfusion, stroke and heart failure. Pulmonary blood pressure can differ substantially from blood pressure in the rest of the body (the so-called systemic circuit) and, as opposed to the latter, can only be measured invasively. Standard techniques, which are based on right-heart catheterization, can have significant side effects, including internal bleeding and partial collapse of the lungs.

Recent advances in physiological modelling allow the pulmonary blood pressure to be predicted from the vasculature geometry and blood flow times series (Qureshi et al.), which can be measured non-invasively with computed tomography (CT) and ultrasound, respectively. The biophysical model depends on various boundary conditions and physiological parameters, most notably the blood vessel stiffness, which can be estimated with computational inference procedures (Paun et al.).

Figure 1 provides a schematic illustration. Given the geometry of the vasculature, most notably the blood vessel diameters (measured with CT), the blood flow (measured with ultrasound) and various boundary conditions (obtained from statistical inference, see Qureshi et al.), the model allows the prediction of the pulmonary blood pressure and the blood vessel stiffness (with the statistical inference techniques described in Paun et al.). In a clinical application, the prediction of high pulmonary blood pressure above a critical threshold will trigger the administration of vasodilators, whose effect is the increase of the vessel diameter. However, as illustrated

TABLE 1. Closed-loop effect and its correction in the biophysical modelling of pulmonary hypertension. Systolic blood flow can be measured with ultrasound; the initial geometry of the vasculature, including the diastolic diameter of the main pulmonary artery (MPA), is available from an initial CT scan. The biophysical model allows the prediction of the pulmonary systolic blood pressure (column 1) and the vessel stiffness (columns 2-3) with the statistical inference procedure described in (Paun et al.). The table shows the relative blood vessel stiffness estimation error (median and 95% posterior credible interval) without (column 2) and with a correction for the closed-loop effect that results from medical interventions triggered by model predictions (column 3). Since this is a simulation study (Qureshi et al.), the true vessel stiffness is known. Computational Bayesian inference was carried out with the MCMC scheme described in Paun et al.

Peak blood pressure exceeding threshold	Relative error without closed-loop correction	Relative error with closed-loop correction
25 %	1.51% (1.04%,1.97%)	-2.0e-03% (-0.37%,0.37%)
50 %	2.52% (2.15%,2.90%)	-1.4e-03% (-0.47%,0.46%)
75 %	61.5% (60.5%,62.4%)	-0.26% (-7.78%,6.49%)

in Figure 1, this causes a closed-loop effect, whereby the prediction from the model causes an action that alters the conditions under which the original prediction was obtained.

3 Simulation study

Our simulations are based on the pulmonary circulation model described in Qureshi et al. The blood vessel geometry of the larger blood vessels has been obtained from a CT scan in a healthy mouse, the effect of the small terminal blood vessels is approximated with electronic circuit (so-called Windkessel) elements consisting of two resistances and a capacitance. This gives three parameters that define downstream boundary conditions of the partial differential equations (PDEs) describing the blood flow through the pulmonary circuit. We also assume that the blood flow at the main pulmonary artery (MPA) is measured (noninvasively with ultrasound), which provides the upstream boundary condition for the PDEs. Following Qureshi et al. and Paun et al., we assume the same stiffness parameter in all blood vessels, which adds one further parameter to the physiological model. We further assume that the blood flows in the two daughter vessels of the MPA are measured (with ultrasound). Our data used for inference are the time courses of the blood flows through three blood vessels. The parameters to be inferred are the vessel stiffness and three Windkessel parameters. Once these parameters have been estimated, the blood pressure in the MPA can be predicted. A graphical illustration is provided in Figure 2 .

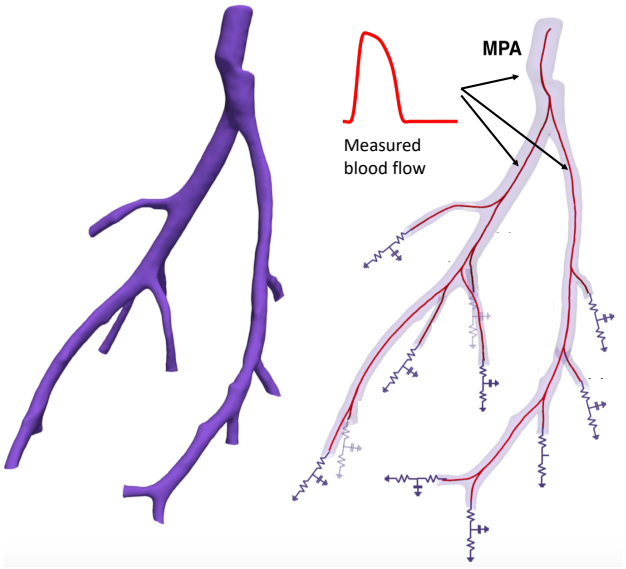

FIGURE 2. *Left panel:* 3D smoothed segmented network from a micro-CT image of a healthy mouse lung. *Right panel:* Directional graph of the same network. Blood flow waveforms are taken from ultrasound measurements at the main pulmonary artery (MPA) and two daughter vessels. At the outlet of each terminal vessel, three-element Windkessel elements with two resistors and a capacitor are attached as boundary conditions to mimic the effect of the microvasculature further downstream.

To simulate the effect of clinical interventions, we monitor the blood pressure in the MPA, and provide an in-silico vasodilator whenever the pressure exceeds a critical threshold. Since this is a proof-of-concept study, we use data from mice rather than humans, and set as an arbitrary threshold the peak pressure found in the hypoxic control mice used in the study of Qureshi et al. We simulate the effect of the vasodilator by increasing the diastolic trough diameter of all blood vessels by the same percentage amount, whose value is determined by the requirement that upon medical intervention, the peak blood pressure in the MPA must not exceed the critical value by more than 5%. This bandwidth defines the uncertainty that remains when explicitly including the closed-loop effect caused by the medical intervention in the model. We compare that with naive parameter inference that does not include any correction for the medical intervention, and assumes the diastolic blood vessel diameter to be fixed. We quantify the effect of ignoring the feedback loop with the percentage estimation error of the vessel stiffness.

4 Results

The results can be found in Table 1. They demonstrate that ignoring the closed-loop effect leads to a systematic bias in the estimation of the blood vessel stiffness, which is a critical risk indicator for vessel wall rupture, stroke and right-ventricle heart failure (Chen et al). Allowing for the medical intervention and including the ensuing feedback loop in the statistical inference corrects this bias and leads to a substantially improved estimation of the stiffness parameter.

5 Conclusions

Quantitative physiological models have great potential for improved and automated clinical decision support. However, it is important to correct for closed-loop effects in model calibration. Using a mathematical toy problem and a realistic fluid dynamics simulation of the pulmonary blood circulation system, we have shown that failing to allow for the effect of medical interventions – and not explicitly including them in the model – can lead to a systematic prediction bias. Our future work will focus on improved statistical inference when data on the effect of medical interventions are noisy and/or partially missing.

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